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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/037350 A1

(54) Title: NEW DRY AND AQUEOUS EPINASTINE-SYRUP-FORMULATION

(57) Abstract: The present invention refers to a new formulation of epinastine in form of a powder (dry syrup) to be mixed with water prior to use. Epinastine can be used either as free base or as a pharmaceutically acceptable salt thereof. Epinastine among others is for treating allergies, pain, in particular chronic pain and inflammation caused pain, migraine, asthma, rhinitis, conjunctivitis and/or bronchitis. In particular, the formulation is for treating allergies, dermatitis, rhinitis, conjunctivitis, bronchitis and asthma.

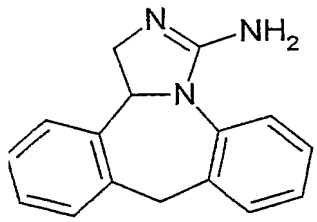
New dry and aqueous Epinastine-Syrup-Formulation

The present invention refers to a new formulation of epinastine in form of a powder (dry syrup) to be mixed with water prior to use. Epinastine among others is for treating allergies, pain, in particular chronic pain and inflammation caused pain, migraine, asthma, rhinitis, conjunctivitis and/or bronchitis (f.e. EP-B-0 035 749, EP 1000623). In particular, the formulation is for treating allergies, dermatitis, rhinitis, conjunctivitis, bronchitis and asthma.

State of the Art

Epinastine, chemically known as 3-Amino-9,13b-dihydro-1H-dibenz-[c,f]imidazol[1,5-a]azepine and its acid addition salts are disclosed for the first time in the German Patent application P 30 08 944.2 which forms the basis for EP 0035749.

Chemically epinastine is represented by the following formula, which does not reflect stereochemical properties:



Epinastine can be used either as free base or as a pharmaceutically acceptable salt thereof. Preferably, epinastine is used as hydrochloride.

If not specified further in the context of the present invention the term epinastine is used for the free base as well as for pharmaceutically acceptable salts.

Methods for its preparations can be taken from EP 0496306 or from WO 01/40229.

Epinastine is marketed in Japan under the brand name Alesion® and most often is used due to its antihistaminic effects.

The state of the art prefers tablets as application form for epinastine.

However, especially for children or the elderly people, tablets are not easy to take and therefore there is a need of new formulation easily applicable by children or elderly people.

Summary of the present invention

It was found that a suitable formulation for such a group of customers like children and the elderly might be liquid formulations. However, it turned out that epinastine has a strong taste of bitterness.

As a consequence there was a need – and to solve this is one objective of the present invention - to develop a neutral or good tasting liquid formulation of epinastine and/or one of its pharmaceutically acceptable acid addition salts.

Another objective of the present invention is to provide a liquid epinastine-formulation which can be stored for some time without the risk of fast decreasing pharmaceutical quality.

Still another objective of the present invention is to create an easy to handle epinastine-formulation for to provide a liquid. Such a liquid formulation shall also be rather a solution than a dispersion in order to improve its acceptance by the patient.

Description of the present invention

The present invention relates to a powder-like formulation (dry syrup) of epinastine, either in enantiomeric, racemic form or a salt thereof, which is mixed with water prior to use. To do so it is required that the powder is dissolved in water very quickly.

In the context of the present invention the term "powder" is used simultaneously with the term "dry syrup" which in turn stands for an essentially water-free admixture of the active form of epinastine, preferably epinastine-hydrochloride, and pharmaceutically acceptable additives and adjuvans necessary to form an aqueous, sweet tasting formulation of the active substance when mixed with water.

Surprisingly, it was found that aqueous formulations of epinastine-hydrochloride cause two different kinds of bad tasting in form of strong bitterness. On one hand there is a quick-acting kind of bitterness and on the other hand there is a lasting bitterness that is tasted for quite a long time.

Unfortunately, the bitter taste of epinastine could not be masked by the use of one conventional taste masking agent as sucrose for example.

In stead it was found that the taste of strong bitterness can be overcome by the combination of quick- and slow acting sweeteners and flavouring agents.

As a consequence thereof a preferred embodiment of the formulation of the present invention should comprise at least one of each kind of these masking agents.

For the masking of quick-acting bitterness, saccharin sodium, erithritol and/or aspartame turned out to be effective. Another suitable group of compounds comprises sugars and suger-derived polyols such as sucrose, D-sorbitol, glycerin and D-mannitol. Preferably, the formulation comprises saccharin sodium, erithritol and/or aspartame. Most preferred is the combination of saccharin sodium, erithritol and aspartame.

The amount of the at least one masking agent for to mask the quick-acting bitterness depends of the agent used.
In case of saccharin sodium, it is between 0.1 % w/w and 2.0 % w/w of the powder formulation. Preferably the amount is 0.8. %

In case of erithritol it is between 50 % w/w and 95 % w/w of the powder formulation. Preferably the amount is 75 to 80 % w/w, most preferred it is 80% w/w.

And in case of aspartame it is between 1 % w/w and 30 % w/w of the powder formulation. Preferably the amount is 5 to 15% w/w, most preferred it is 10%.

For masking the lasting bitterness glycyrrhizinates were found to be highly effective. Among them glycyrrhizinic acid and/or monoammonium glycyrrhizinate are the preferred ones. The most preferred one is monoammonium glycyrrhizinate.

The amount of monoammonium glycyrrhizinate in the powder formulation is 0.1 % w/w and 3.0 % w/w of the powder formulation. More preferred are 0.1 to 1% w/w and most preferred is 0.6%.

The formulation further may comprise adjuvans, among which are for example pH-adjusting agents. It is preferred to add such pH-adjusting agents to adjust the pH of the resulted liquid to a value of between 5 and 8, preferably 6 and 7. Among those agents are citric-acid, succinic acid, tartaric acid, acetic acid, citrates, acetates, vitamin C, hydrochloric acid, carbonates, phosphates, disodium phosphate, monosodium phosphate, sodium-, calcium-, potassium- and/or magnesium-hydroxide. Preferred are buffer substances like disodium phosphate.

Further commonly other used additives can optionally be added, too.
Among these are

- binding agents such as hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, starch, dextrin, gelatine and polyvinylpyrrolidone, preferably hydroxypropylcellulose,
- flow agents such as hydrated silicon dioxide, light anhydrous silicic acid,
- odorizors such as sunfix orange No.22734 (commercial name, sunfix orange which is preferred contains orange flavour (30%w/w), acacia (30%w/w) and dextrin(40%w/w)), orange oil, mentha oil, eucalyputus strawberry flavour, vanilla flavour, yoghurt flavour and other flavours known in the art,
- colour pigments such as food yellow No.5, also being known as sunset yellow FCF (disodium salt of 6-hydroxyl-5-(4-sulfophenylazo)-2-naphthalenesulfonic acid), the latter being preferred, ferric oxide, and other food colour pigments, f.e. the ones known in Japan as food red No.3, 102,105 and 106, food yellow No.4 and other food colours known in the art, and/or
- preservatives such as benzoic acid, salts thereof, preferably sodium benzoate, paraoxybenzoic acids, salts thereof and other known preservatives, whereby sodium benzoate is preferred and
- effervescent agents such as bicarbonate.

The amount of epinastine or its salt is between 0.5 % w/w and 5 % w/w of the powder formulation. More Preferred is an amount of between 0,5 % w/w and 2 % w/w, the most preferred amount is 1 %.

The powder formulation preferably does not contain an active substance which is not epinastine or a pharmaceutically acceptable salt thereof.

The active substance, preferably epinastine-hydrochloride and all the additives are mixed to a powder and than the powder is mixed with water to preferably obtain a liquid formulation. Although the liquid formulation may either be a solution, suspension or a colloid, the preferred liquid formulation is a transparent and clear aqueous solution.

It is preferred to mix the powder formulation with water to obtain a liquid having a concentration of between 250mg per 5-50ml and 2000mg per 10-100 ml , preferably the amount is between 50 mg per 10 ml and 2000mg per 10ml.
If epinastine-hydrochlorid is used, the amount in the context of the present invention is (about) the same as for the free base.

In order to ensure that the patient easily can prepare the liquid formulation the inventive powder formulation (dry syrup) can be delivered in certain packages. In these packages the water and the inventive powder formulation are stored separately from each other. The package further allows the both components to mix in an easy way.

As a consequence thereof the present invention also relates to a kit comprising two components, a) the inventive powder formulation and b) water, both components separated from each other.

In the state of the art several bottles having special caps are known to solve this issue. Most often in such packages the liquid solvent can be stored in a bottle of glass, plastic, metal and so on while the cap for closing the bottle comprises a chamber to take the dry powder formulation. Prior to use the patient can take of the powder of the cap and mix it with the water in the bottle. This mixing process can either be done consciously, meaning the patient actively takes the powder and puts it into the water. In other embodiments the patient can initiate the mixing process in a more automatic way by for example just screwing, pressing, shaking the cap or the bottle in order to put away a barrier in the chamber containing the powder and by doing so allowing it to fall from the cap into the bottles.

Such packagings are disclosed for example in EP 0599189, EP 0344849, EP 0217425, EP 0093090, US 3802604 and others. Herewith, all of these devices are incorporated by reference. Other, similar devices might be used, too.
Besides, such package forms the dry syrup formulation can be stored in an aluminium or plastic-bag or in an aluminium or plastic bottle. The such stored powder then can be used with a pre-metered amount of water, stored in another package or the freshly filled drinking water is used.

Other package systems may be used, too.

In the context of the present invention the powder formulation can also be pressed to tablet to be dissolved in water, for example an effervescent tablet. In such an embodiment the tablet – just as the powder formulation - may additionally comprise an effervescent agent such as bicarbonate.

Experimental

New dry and aqueous epinastine- Syrup-Formulation 0.5%.

Powder-Formulation No.	1	2	3	4	5	6	7
epinastine hydrochloride [mg]	5	5	5	5	5	5	5
glycerin [mg]	0	0	0	0	0	0	350
sucrose [mg]	0	0	0	0	0	540	620
anhydrous citric acid [mg]	0	0	0	0	0	25	0
monoammonium glycyrrhizinate [mg]	7	0	6	6	6	0	0
saccharin sodium [mg]	0	6	4	0	5	5	0
sodium fumarate [mg]	10	10	0	10	5	0	10
disodium phosphate [mg]	0	0	0	3	15	10	0
erithritol [mg]	923	919	925	916	904	395	0
aspartame [mg]	60	60	60	60	60	25	0
sodium benzoate [mg]	0	0	0	0	0	0	15
Results							
Appearance when mixed with water*	white	clear#	white	clear#	clear#	clear#	clear#
Masking of Bitterness	good	good	good	good	very good	good	good

* the amount of water is not significant. However, 1g of powder preferably should be readily soluble in 5-50 ml of water.

Clear in the meaning of transparent.

New dry and aqueous epinastine-Syrup-Formulation 1.0%

Powder-Formulation No.	8	9	10	11	12	13	14
epinastine hydrochloride [mg]	10	10	10	10	10	10	10
glycerin [mg]	0	0	0	0	0	0	350
sucrose [mg]	0	0	0	0	0	542	425
anhydrous citric acid [mg]	0	0	0	0	0	25	0
monoammonium glycyrrhizinate [mg]	10	0	10	6	6	0	0
saccharin sodium [mg]	0	10	5	0	8	0	0
sodium fumarate [mg]	20	10	0	15	5	0	10
disodium phosphate [mg]	0	0	0	10	15	0	0
erithritol [mg]	859	859	854	838	835	397	200
aspartame [mg]	100	100	100	100	100	25	0
hydroxypropylcellulose [mg]	0	20	20	20	20	0	0
hydrated silicon dioxide [mg]	1	1	1	1	1	1	0
Odorizor* [mg]	0	(1)	(1)	(1)	(1)	(1)	0
food yellow No.5** [mg]	0	(0.05)	(0.05)	(0.05)	(0.05)	(0.05)	0
sodium benzoate [mg]	0	0	0	0	0	0	5
Results							
Appearance when mixed with water***	white	clear#	white	clear#	clear#	clear#	clear#
Masking of Bitterness	good	good	good	good	very good	good	good

*sunfix orange No.22734 (commercial name) containing orange flavor (30%w/w), acacia (30%w/w) and dextrin (40%w/w).

** *Another name of Food yellow no.5 is sunset yellow FCF (disodium salt of 6-hydroxyl-5-(4-sulfophenylazo)-2-naphthalenesulfonic acid.*

*** the amount of water is not significant, however, 1g of powder preferably should be readily soluble in 10-100 ml of water.

Clear in the meaning of transparent.

Claims

1. Pharmaceutical powder formulation comprising an active agent based on epinastine and/or an acid addition salt, preferably the hydrochloride, at least two kinds of sweeteners and/or flavourings and optionally further pharmaceutically acceptable adjuvans, whereby one of the at least two kinds of sweeteners and/or flavourings is for to mask the quick-acting bitterness of the active agent and the other one is for to mask the long-acting bitterness of the active agent.

2. Pharmaceutical powder formulation according to claim 1, characterised in that the at least one sweetener and/or flavouring for to mask the quick-acting bitterness is selected from saccharin sodium, erithritol, aspartame and/or sugars or other polyols such as sucrose, glycerin, D-sorbitol and D-mannitol.

3. Pharmaceutical powder formulation according to claim 1 or 2, characterised in that the at least one sweetener and/or flavouring for to mask the quick-acting bitterness is selected from saccharin sodium, erithritol and aspartame.

4. Pharmaceutical powder formulation according to claim 1 to 3, characterised in that the at least one sweetener and/or flavouring for to mask the quick-acting bitterness is a combination of saccharin sodium, erithritol and aspartame.

5. Pharmaceutical powder formulation according to any of claims 1 to 4, characterised in that the at least one sweetener and/or flavouring for to mask the long-acting bitterness is a glycyrrhizinate or glycyrrhinic acid, preferably selected from mono-, di-ammonium glycyrrhizinate, di-, tri-sodium glycyrrhizinate and/or dipotassium glycyrrhizinate, most preferably monoammonium glycyrrhizinate.

6. Pharmaceutical powder formulation according to any of claims 1 to 5, characterised in that the formulation further comprises a pH-adjusting agent selected from the group of citric-acid, citrates, succinic acid, tartaric acid, acetic acid, acetates, vitamine C, hydrochloric acid, carbonates, sodium-, calcium-, potassium- and/or magnesium- hydroxide, phosphates, preferably disodiumphosphate and/or monosodium phosphate, most preferably monosodium phosphate.

7. Pharmaceutical powder formulation according to any of claims 1 to 6, characterised in that the formulation further comprises at least one adjuvans selected from the group of odorizers, colour pigments, preservatives, flow agents and/or binding agents.

8. Pharmaceutical powder formulation according to any of claims 1 to 7, characterised in that the formulation comprises epinastine-hydrochloride in an amount of between 0.5% w/w and 5 %w/w, saccharin sodium in an amount of between 0.1 % w/w and 2.0 % w/w, erithritol in an amount of between 50 % w/w and 95 % w/w, aspartame in an amount of between 1 % w/w and 30 % w/w, monoammonium glycyrrhizinate in an amount of 0.1 % w/w and 3.0 % w/w and optionally disodiumphosphate, sodium fumarate, hydroxypropylcellulose, hydrated silicon dioxide, orange flavor, acacia, dextrin and /or disodium salt of 6-hydroxyl-5-(4-sulfophenylazo)-2-naphthalenesulfonic acid.

9. Pharmaceutical powder formulation according to any of claims 1 to 8, characterised in that the formulation comprises epinastine hydrochloride, monoammonium glycyrrhizinate, saccharin sodium, sodium fumarate, erithritol, aspartame, hydroxypropylcellulose, hydrated silicon dioxide, orange flavour, acacia, dextrin and disodium salt of 6-hydroxyl-5-(4-sulfophenylazo)-2-naphthalenesulfonic acid.

10. Pharmaceutical powder formulation according to any of claims 1 to 9, characterised in that the formulation comprises an effervescent agent.

11. Pharmaceutical tablet, comprising the ingredients of the powder formulation according to any of claims 1 to 10.

12. Liquid formulation available by mixing any of the powder formulations of claims 1 to 10 or the tablet of claims 11 with water.

13. Liquid formulation according to claim 12, characterised in that the formulation is a solution.

14. Liquid formulation according to claim 13, characterised in that the formulation is a dispersion.

15. Liquid formulation according to claim 12 or 13, characterised in that the formulation comprises a pH-adjusting agent according to claim 6 in an amount to adjust the pH to between 5 and 8, preferably to between 6 and 7.

16. Liquid formulation according to any of claims 12 to 15, characterised by an amount of epinastine of between 0.09 mg and 35 mg per 10 ml, preferably of between 0.4 mg and 18 mg per 10 ml.

17. Liquid formulation according to any of claims 12 to 15, characterised by an amount of epinastine-hydrochloride of between 0.1 mg and 40 mg per 10 ml, preferably of between 0.5 mg and 20 mg per 10 ml.

18. Liquid formulation according to any of claims 12 to 17, characterised in that 250 mg to 2000 mg of a powder formulation according to any of claims 1 to 9 or the tablet of claim 11 are mixed with 10 to 100 ml of water.

19. Package comprising a kit of a powder formulation according to any of claims 1 to 10 or the tablet of claim 11 and separated thereof water to obtain a liquid formulation according to any of claims 12 to 18 if the powder and the water are mixed together.

20. Package according to claim 19, characterised in that the package is a bottle with a cap comprising a chamber, that can be opened easily in a manual way or by screwing or pressing the cap onto the bottle, the chamber containing a powder formulation according to any of claims 1 to 10 or the tablet of claim 11 and the bottle comprising the water.

21. Use of a powder formulation according to any of claims 1 to 10 or use of the tablet of claim 11 to mix with water to obtain a formulation according to any of claims 12 to 18.

22. Use of a formulation according to any of claims 1 to 18 for to manufacture a medical preparation for to treat allergies, pain, in particular chronic pain and inflammation caused pain, migraine, asthma, rhinitis, conjunctivitis and/or bronchitis, preferably for to treat allergies.

23. Method of treating allergies, pain, in particular chronic pain and inflammation caused pain, migraine, asthma, rhinitis, conjunctivitis and/or bronchitis, preferably for to treating allergies characterised by mixing a powder formulation according to any of claim 1 to 10 or the tablet of claim 11 with water to obtain a liquid formulation according to any of claims 12 to 18 and to apply this formulation to a patient.

24. Process for making a powder formulation according to any of claims 1 to 10 by mixing the different components together.

25. Process for making a tablet according to claim 11 by mixing the different components together and subsequent pressing thereof.

26. Process for making a liquid formulation according to any of claims 12 to 18 by mixing the powder formulation according to any of claims 1 to 10 or the tablet according to claim 11 with water.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/11250

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/55 A61K9/00 A61K9/14 A61K9/20 A61K47/26
A61P11/02 A61P11/06 A61P27/02 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, MEDLINE, EMBASE, BIOSIS, PASCAL, SCISEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 020 193 A (DAIICHI SEIYAKU CO) 19 July 2000 (2000-07-19) page 2, line 33-36 page 3, line 51,52 claims 3,7,17,18	1-26
X	EP 0 658 340 A (UNILEVER PLC ;UNILEVER NV (NL)) 21 June 1995 (1995-06-21) page 2, line 55 -page 3, line 8	1
A	PATENT ABSTRACTS OF JAPAN vol. 1997, no. 06, 30 June 1997 (1997-06-30) & JP 09 052849 A (TAISHO PHARMACEUT CO LTD), 25 February 1997 (1997-02-25) abstract	1-26

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 2002	18/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Zimmer, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/11250

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 942 503 A (JUNG BIRGIT ET AL) 24 August 1999 (1999-08-24) column 6; claims 1-3	1-26

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ırnational application No.
PCT/EP 02/11250

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy Although claims 22,23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/11250

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 1020193	A	19-07-2000	AU	9187598 A	23-04-1999
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